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Association between treatment planning and delivery factors and disease progression in prostate cancer radiotherapy: Results from the TROG 03.04 RADAR trial

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ABSTRACT

Background and purpose: To evaluate the impact of treatment planning and delivery factors on treatment outcome as measured by post-treatment disease progression.

Materials and methods: Accruing 813 external beam radiotherapy participants during 2003–2007, the RADAR trial collected a comprehensive range of clinical treatment factor data for each participant. Both the Fine and Gray competing risks modelling and the Kaplan–Meier (KM) analysis were undertaken to determine the impact of these factors on local-composite progression (LCP), with 709 participants available for analysis.

Results: Participants with treatments involving 7 or more beams experienced significantly higher incidence of LCP, with a sub-hazard ratio (relative to 3-beam participants) of 3.056 (CI: 1.446–6.458, $p < 0.0034$). Participants treated with a more rigorous dose calculation algorithm also displayed significantly higher incidence of LCP, with a sub-hazard ratio of 1.686 (CI: 1.334–2.132, $p < 0.0001$). The KM analysis resulted in the same groups showing a higher incidence of LCP, with log-rank test results of $p = 0.0005$ and $p = 0.0008$ respectively.

Conclusions: The RADAR dataset has enabled a successful secondary analysis in which the impact of technical modifications has been assessed, challenging several established hypotheses. Increasingly precise treatments should be complemented with increasing accuracy to avoid potential geometric miss.

Treatment planning studies, based on planned dose distributions, are commonly used to evaluate improvement from technical modifications to radiotherapy treatment [1]. In determining the effects of these modifications on treatment outcome, such studies typically assume more precise or conformal dose distributions are clinically advantageous. More conformal treatments, however, have been found to be associated with increased clinical failure, particularly in high-risk prostate cancer patients [2]. Modifications leading to more conformal dose distributions will therefore not necessarily lead to improved treatment outcomes. Clinical evidence based on actual patient outcomes would help to resolve and rationalise the actual effects of these treatment factors.

Planning studies have generated multiple hypotheses regarding the impact of modifying treatment related factors. For example, the use of a more rigorous dose calculation algorithm (DCA), with the ability to correct for tissue inhomogeneity, has been proposed to have a negligible effect on treatment outcome in the context of prostate cancer treatment, due to two factors. Firstly, more rigorous DCAs have resulted in a dose reduction to the planning target volume (PTV) of only 3% relative to that of less sophisticated algorithms [3]. Secondly, it is apparent that the pelvic region contains mostly homogenous tissue [4]. The planning effects of patient setup orientation have also been investigated [5,6], with patients treated in the prone position requiring a larger PTV, resulting in increased dose to critical organs but more dose coverage to the tumour region, which may reduce treatment failure. Moiseenko et al. evaluated the effects of bladder filling on dose–volume distributions for the prostate and surrounding healthy organs [7], showing that patients with a full bladder (relative to those with an empty bladder) received less dose to healthy organs but similar dose to the prostate region. This suggests improved conformity

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with potentially no decrease in tumour control. Studies investigating the impact of rectal distension (expansion) due to filling have demonstrated no significant relationship with prostate stability [8], while there is substantial evidence showing an increase in biochemical and clinical failure in patients with a distended rectum (due to filling) at planning [9–11].

This study provided a unique opportunity to test the impact on treatment outcome of several clinical factors associated with treatment planning and delivery, in the context of a large multicentre prostate radiotherapy clinical trial. Data were derived from the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) trial [12–14], which examined the impact of duration of androgen suppression (AS) on intermediate and high-risk prostate cancer patients. An extensive technical quality assurance and data collection scheme [15,16] ensured a comprehensive range of clinical data was recorded for each trial participant. Covariates describing treatment planning and delivery factors were generated, while patient time-to-event data were used to produce an indicator of post-treatment outcome – local composite progression (LCP), while accounting for competing events [17]. This study aimed to determine the associations between the clinical covariates and treatment efficacy (LCP) in the RADAR dataset.

Methods and materials

RADAR trial

The RADAR trial (TROG 03.04), accruing between 2003 and 2007, tested the hypothesis that 12 months of adjuvant androgen deprivation therapy (ADT) starting immediately after standard therapy (i.e. 6 months of ADT before and during radiotherapy) will improve patient treatment efficacy when compared with standard radiotherapy alone [12,13]. Participants were divided into four treatment arms: those receiving short-term (6 months) androgen suppression only (STAS), STAS and 18 months of zoledronate (STAS + Z), intermediate-term (18 months) androgen suppression only (ITAS), and ITAS and zoledronate (ITAS + Z).

Recruited participants had either intermediate-risk (T2a) or high-risk (T2b+) prostate cancer, undergoing dose-escalated external beam radiotherapy (EBRT) with prescription doses of 66, 70 or 74 Gy, or 46 Gy EBRT combined with a brachytherapy boost. Twenty-three centres accrued participants across Australia and New Zealand. A comprehensive set of clinical covariates, describing important aspects of patient anatomy, treatment planning and delivery, was recorded at each centre for each trial participant. RADAR was the first TROG trial to incorporate full electronic review of the treatment planning data of accrued participants [15].

Patient outcomes

One participant outcome (endpoint) was derived from trial data as part of this analysis: local composite progression (LCP). LCP was defined as the post-treatment occurrence of either local/clinical failure (LF) or PSA progression (defined per the Phoenix definition [18]), with a PSA concentration doubling time between 6 and 100 months. The Fine and Gray competing risks (FGCR) analysis considered the following as competing events: distant progression alone >2 months before LF; PSA doubling time <6 months or >100 months after PSA progression; early secondary therapy. For the Kaplan–Meier analysis, which cannot account for competing events, if the participant died or reached the end of follow-up before a relevant event occurred, they were censored.

Variables

Several treatment-related clinical covariates were included in the analysis. Variables were generally defined in categorical form, with either multiple categories or binarized about the median variable value. Tables 1–3 contain variable definitions and relevant information such as hypothesised effects. The variables were split into four groups, the 'clustering adjustment variable' (Table 1), 'control variables' (Table 1), 'patient anatomical and setup variables' (Table 2), and 'treatment planning variables' (Table 3).

Control variables are included in the FGCR models to remove their confounding influence upon LCP, resulting in a clearer picture of the impact of the subject variables on LCP and hence treatment outcome. The subject variables, shown in Tables 2 and 3, represent several clinical covariates associated with patient anatomy, treatment planning and delivery. The impact of these variables on LCP is the focus of this study.

Table 1
Clustering adjustment and control variable information.

Name	Symbol	Description	Categories
Clustering Adjustment Variable			
Treatment Centre	P_{Centre}	The centre at which the trial participant is treated	A separate category for each of the 23 centres.
Control Variables			
Age at Randomisation	P_{Age}	The participant's age at trial randomisation	Continuous, Mean = 68.65, SD = 6.56 years
EBRT Start Date	P_{EBRTSD}	The date of the start of EBRT for the participant	[353] 1: <Med (27/03/2006) [356] 2: ≥Med
Risk Group	P_{GS}	The participant's risk group determined by Gleason's score	[496] 1: Gleason's score ≤ 7 [213] 2: Gleason's score >7
Dose Group	P_{Dose}	The prescribed dose for the participant's EBRT treatment	[91] 1: 66 Gy [395] 2: 70 Gy [223] 3: 74 Gy
Cancer Stage Group	P_{Stage}	The participant's prostate cancer stage group.	[508] 1: T2 [201] 2: T3/T4
Treatment Arm	P_{Arm}	The trial arm in which the participant was treated.	[182] 1: STAS [176] 2: STAS + Z [176] 3: ITAS [175] 4: ITAS + Z
Baseline PSA Group	P_{PSA}	The participant's PSA group as per PSA concentration at randomisation.	[496] 1: PSA ≤ 20 ng/mol [213] 2: PSA > 20 ng/mol

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